Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Lymphoblastic Leukemia (ALL)

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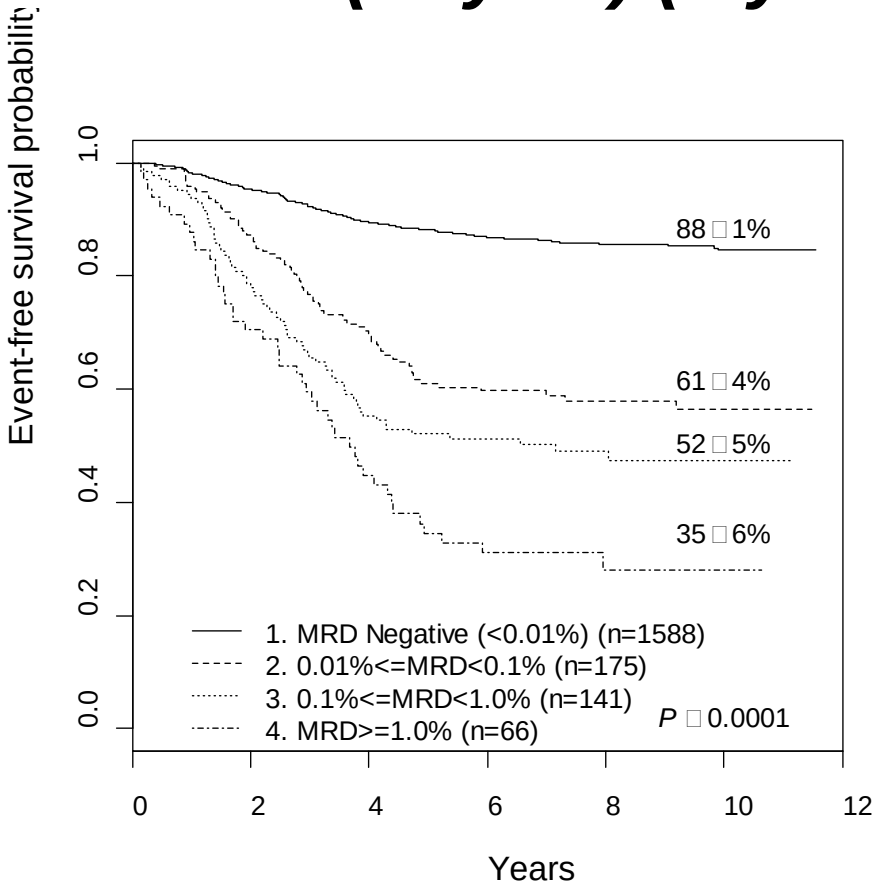
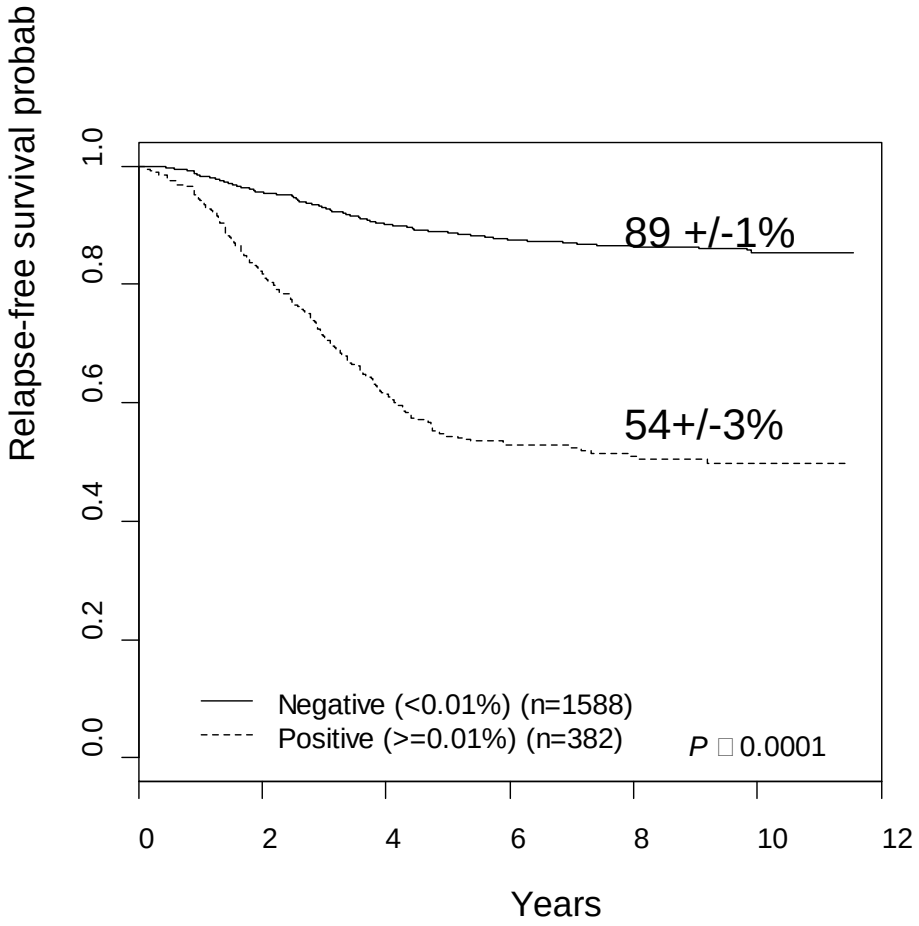
Trials in Newly diagnosed pediatric ALL P9900

End induction MRD (Day 29) (5-year EFS)



Overall RFS by MRD at end of induction



P9900

MRD status	No relapse	Relapse	Total
Negative (<0.01%)	1383 87.09	205 12.91	1588
Positive (>=0.01%)	205 53.66	177 46.34	382

Variable	Hazard ratio	P
Delayed intensification	0.777	0.0338
Day 29 MRD >=0.01%	3.896	<0.0001
Day 8 MRD>=1.0%	1.335	0.0165
NCI high risk	2.239	<0.0001
Trisomies 4 and 10	0.543	<0.0001
TEL-AML1	0.821	0.2072

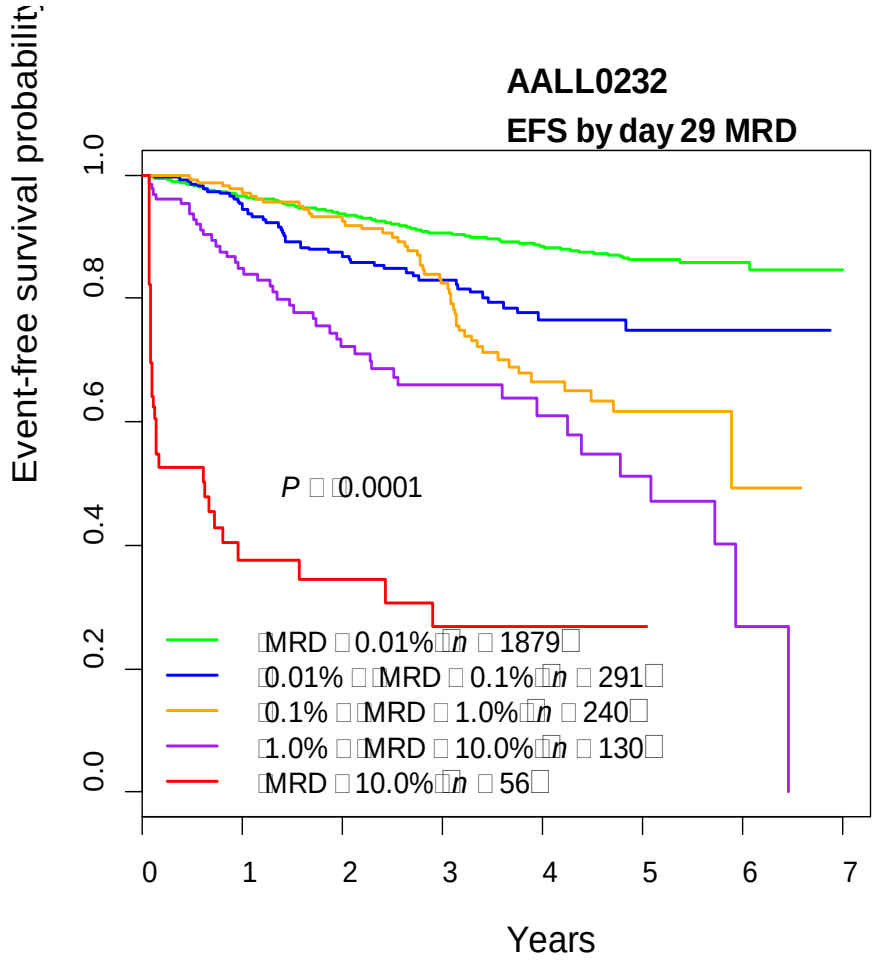
COG AALL0232 – Phase III trial for NCI High Risk ALL

- Initially 2x2 Factorial design (steroid - D vs P, and MTX- H vs C randomization)
- Later Steroid randomization restricted to <10 yr olds, while MTX randomization included all age groups
- Trt arms PC, PH, DC, DH
- Interim analyses showed HDMTX was more efficacious than Capizzi MTX overall (5-year EFS 82% vs 75%, p=0.006)

AALL0232

- **Among <10 yr olds, significant interaction between the two study questions. Hence compared the four arms. Since HDMTX was shown to be superior to Capizzi overall, the comparison was restricted to DH vs. PH. DH was superior to PH for <10 year olds**
  - 5-year EFS 87+/-5% vs. 80+/-6%, p=0.0162
  - MRD negative rates DH: 81% vs. PH: 83% (similar)
  - Clearly MRD not a surrogate in this case, but is highly prognostic both overall and within treatment regimens

AALL0232
MRD



MRD as a surrogate

- **Early time point?**
- **sensitivity (0.01%?)**
- **In high risk ALL subsets?**
  - Relapsed ALL
  - Infants
- **Patients with specific high risk markers**
  - Ph+ ALL, JAK mutations…

MRD as surrogate

- **Early phase trials for targeted therapies**
  - New agents introduced early in therapy (induction)
  - Assess activity / efficacy using MRD as a surrogate of EFS
  - Use early endpoint in screening trials of more than one new agent - quicker results

MRD as surrogate

- **Develop Adaptive trial designs using surrogate end points - example**

  Renfro LA, Carlin BP, Sargent DJ (2012), Bayesian Adaptive Trial design for a Newly Validated Surrogate endpoint, Biometrics 68, 258-267.

  Allows new surrogate endpoint to be primary in assessing effect of an intervention. Using multi-trial historical information on the validated relationship between surrogate and clinical endpoints.

MRD as surrogate

- **Evaluate accumulating data as trial progresses, against this relationship, thus guarding against an erroneous assessment of treatment effect based on a truly invalid surrogate.**
- **When joint outcomes on the new trial are in line with what was seen on historical trials, proceed with surrogate endpoint as the primary endpoint, adaptively –**
  - With rules for stopping the study for early success, inferiority of experimental regimen, futility.
- **Otherwise discard surrogate and use adaptive rules to the original primary endpoint**